



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :  A61K 35/20		A1	(11) International Publication Number:  WO 98/11904																		
			(43) International Publication Date: 26 March 1998 (26.03.98)																		
(21) International Application Number: PCT/GB97/02572 (22) International Filing Date: 19 September 1997 (19.09.97) (A0) Priority Date: 9619634.0 20 September 1996 (20.09.96) GB		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW. ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).																			
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(74) Agent: ATKINSON, Peter, Birch, Marks & Clerk, Sussex House, 83-85 Mosley Street, Manchester M2 3LG (GB).																					
(54) Title: PREVENTION OF GASTROINTESTINAL DAMAGE																					
(57) Abstract <p>Colostrum or a derivative thereof is used for the prophylactic treatment of a gastrointestinal condition partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug, e.g. indomethacin.</p>																					
<table border="1"> <caption>Data extracted from the bar chart</caption> <thead> <tr> <th>Group</th> <th>Condition</th> <th>Mean Villus Height (mm)</th> <th>Standard Deviation (mm)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Control</td> <td>Undamaged</td> <td>~0.75</td> <td>~0.05</td> </tr> <tr> <td>indo</td> <td>~0.60</td> <td>~0.05</td> </tr> <tr> <td rowspan="2">10% Colos</td> <td>Undamaged</td> <td>~0.72</td> <td>~0.05</td> </tr> <tr> <td>indo</td> <td>~0.65</td> <td>~0.05</td> </tr> </tbody> </table>				Group	Condition	Mean Villus Height (mm)	Standard Deviation (mm)	Control	Undamaged	~0.75	~0.05	indo	~0.60	~0.05	10% Colos	Undamaged	~0.72	~0.05	indo	~0.65	~0.05
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PREVENTION OF  
GASTROINTESTINAL DAMAGE.

The present invention relates to the prevention of gastrointestinal damage and more particularly, but not exclusively, to such damage which occurs in the intestine.

There are a variety of gastrointestinal conditions in which damage to epithelial type cells occur. For example, this damage may be in the form of ulceration, increased permeability with protein and blood loss from the intestine or structuring.

Gastrointestinal conditions involving damage to epithelial cells arise after prolonged administration of Non Steroidal Anti-inflammatory Drugs (NSAIDs) (e.g. indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac, aspirin etc) to patients who require protection from chronic inflammatory medical conditions. Examples of such chronic conditions which require prolonged administration of NSAIDs are rheumatoid arthritis and osteoarthritis. NSAID therapy is also beneficial for sufferers of Cystic Fibrosis (to ameliorate the inflammatory process causing lung damage). Long term use of NSAIDs is associated with a high risk of developing gastric or intestinal damage including structuring, fibrosis and ulceration. A major effect of NSAIDs is damage to gastrointestinal epithelial cells which may lead to the development of ulcers. Such ulcers may unexpectedly haemorrhage or become perforated. This leads to the requirement for emergency treatment and when undetected may even be associated with mortality. Mortality is especially associated with patients on NSAIDS who perforate because these patients are often symptomless and do not suffer pain because of the pain dampening effects of NSAIDs.

Up to 60% of NSAID-taking patients complain of dyspepsia or generalised abdominal discomfort. It has also been reported that gastric ulceration occurs in 12-30%, and duodenal lesions in 2-19% of long term NSAID users. When it is considered that NSAIDs account for 5% of prescribed drugs in the UK but account for 25% of all reported adverse effects, it is apparent that these adverse effects associated with NSAIDs are a major problem and that a satisfactory means of preventing

NSAID-induced damage to gastrointestinal epithelial cells would be of considerable benefit.

Various measures are used to treat NSAID-induced ulcers. These include the use of several types of pharmaceutical products, such as Histamine H<sub>2</sub> receptor antagonists, sucralfate, prostaglandins (e.g. misoprostol) and hydrogen-potassium pump inhibiting agents (e.g. omeprazole). A major disadvantage of these products is that, although they are effective at treating gastric damage, they are largely ineffective when directed towards intestinal epithelium. It is therefore desirable that there is an agent which is effective for intestinal epithelium. It is particularly desirable that there is a suitable agent that may be used prophylactically to prevent gastrointestinal damage occurring. For instance, it would be of great benefit to treat someone prophylactically if it is anticipated they will require NSAID therapy in order that gastrointestinal damage may be avoided. For example, prophylactic treatment would be of benefit for sufferers of rheumatoid arthritis, osteoarthritis or cystic fibrosis who are taking NSAIDs.

It is an object of the present invention to obviate or mitigate the above mentioned disadvantages and provide a prophylactic agent that may be used to prevent damage occurring to gastrointestinal epithelium as a result of administration of NSAIDs.

According to a first aspect of the present invention, there is provided the use of colostrum or a derivative thereof for the manufacture of a medicament for prophylactic treatment of a gastrointestinal condition partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug.

According to a second aspect of the present invention, there is provided a method for the prophylactic treatment of a gastrointestinal condition that is at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug, the method comprising administering to a person or animal in need of such treatment a therapeutically effective amount of colostrum or derivative thereof.

By "prophylactic treatment" we mean either (i) a treatment that protects gastrointestinal epithelium such that a gastrointestinal condition that is at least partially characterised by damage to epithelial cells does not occur; or (ii) a treatment that prevents healthy epithelial cells from becoming damaged if a gastrointestinal condition already exists.

The invention is applicable for prophylactic treatment of patients who are at risk of suffering NSAID induced damage to gastrointestinal epithelial cells (such as sufferers of rheumatoid arthritis, osteoarthritis or cystic fibrosis who are taking NSAIDs). Therefore colostrum or a derivative thereof may be used to prophylactically prevent damage caused by NSAIDs such as indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac or aspirin.

The colostrum used in the invention is preferably bovine colostrum. Preferred colostrum derivatives are therefore derivatives of bovine colostrum.

Colostrum is the milk secreted by the mammary gland during the first 48 hours following parturition. The composition of this "first milk" is fundamentally different to that of the subsequently secreted normal milk. In particular, colostrum contains increased concentrations of growth hormones, growth factors and maternal immunoglobulins. The colostrum used in the present invention is preferably the milk obtained in the first 2 milkings following parturition. Derivatives of such milk may also be used.

The colostrum derivatives referred to in this invention are those which contain viable immunoglobulins, growth factors and /or growth hormones as may be found in colostrum. Examples of preferred colostrum derivatives are:

1. Colostrum that is spray dried to form a powder before being used. If desired the spray dried derivative may be reconstituted in the form of a spray dried skimmed milk drink. The colostrum may be defatted before spray drying if desired.
2. Colostral whey or a derivative thereof. Colostral whey is colostrum from which casein proteins have been removed. Derivatives suitable for use according to the invention include ultrafiltered or microfiltered fractions of colostral whey. These fractions contain more concentrated Growth Factors relative to remaining colostral

proteins and nutrients. Colostral whey may be used in liquid form (which may be defatted if desired) or may be further treated (such as being spray dried) before use according to the invention.

As stated above, it is most preferred that the colostrum used in the present invention is bovine colostrum. The colostrum may be obtained by normal milking procedures, after which it may be pooled and frozen prior to being processed, if desired, to produce a colostrum derivative.

We have found that colostrum, or a derivative thereof, has the beneficial effect of preventing gastrointestinal epithelial cells from being damaged. These beneficial effects are surprising when it is considered that in our studies normal milk, or a derivative thereof, is significantly less effective for preventing such damage.

Colostrum contains significantly higher levels of physiologically active agents such as hormones, Growth Factors and Immunoglobulins than can be found in normal milk and while we do not want to be bound by any theory, we believe this may contribute towards its efficacy in preventing the development of the abovementioned conditions. We believe these agents within colostrum, or a derivative thereof, protect epithelial cells from damage being inflicted upon them (thereby acting as a prophylactic). It is also possible that these physiologically active agents found in colostrum, or a derivative thereof, regulate apoptosis or regulate modelling of the extracellular matrix in the gastrointestinal tract.

The use of colostrum, or a derivative thereof, has many advantages over therapies currently being used for NSAID induced gastrointestinal conditions that are characterised by epithelial damage. For instance, large quantities of bovine colostrum can be readily obtained from dairy cattle. This means there are sufficient resources for the wide scale prophylactic use of colostrum to help patients who are on long term NSAID therapy. Furthermore, bovine colostrum is a natural and safe resource.

The colostrum or derivative thereof is preferably administered by an enteral route. This may be by means of an enema, an asogastric tube or alternatively by means of gastrostomy tubes or jejunostomy tubes. A most preferred route of administration is by an oral route.

It is preferred that colostrum, or a derivative thereof, is administered at least once daily. Treatment with colostrum or derivatives thereof may continue until the risk of gastrointestinal damage occurring has been removed. It is also preferred that the colostrum or a derivative thereof is administered from 6 to 72 (more preferably from 24 to 48) hours in advance of initiation of NSAID therapy and should ideally continue until NSAID therapy has stopped.

The amount of colostrum, or derivative thereof, to be administered for prophylactic treatment of an NSAID induced gastrointestinal condition that is at least partially characterised by damage to epithelial cells depends on a number of factors. These include, for example, the particular colostrum or derivative to be administered, the severity of the condition, and the age of the subject, to be treated.

We have established that, to have a protective effect on gastrointestinal epithelium, bovine colostral whey is preferably administered in the range of 30-300mls/day. 0.1-60.0 grammes/day represent a suitable daily dosage of spray dried derivatives of bovine colostrum. It will be appreciated that the amount of a colostrum derivative required will depend upon the precise extraction or purification steps undertaken to prepare such a colostrum derivative.

If desired, the colostrum (or derivative thereof) may be supplemented with one or more growth factors (e.g. purified growth factors) such as an IGF (e.g. IGF-1 or IGF-2), a transforming growth factor (e.g. TGF $\beta$ 1, TGF $\beta$ 2 or TGF $\beta$ 3), a keratinocyte growth factor, a fibroblast growth factor, or a platelet-derived growth factor.

Colostrum, or a derivative thereof, may be formulated with other agents to form a composition suitable for enteral consumption. For instance, agents such as carbohydrates, a nitrogen source, vegetable oils, emulsifiers, oils containing long chain fatty acids, antioxidants, vitamins, soluble fibre or minerals and other trace elements may be included in the composition to fulfil nutritional requirements when colostrum is being incorporated into a food product (such as a confectionery bar) or drink product (in which case a liquid derivative or a powder derivative reconstituted as a liquid may be used). Alternatively derivatives of colostrum may be formulated

with suitable excipients, stabilizers and the like to make a tablet, capsule or liquid medicament.

Additionally flavouring may also be included to make such compositions more palatable if the medicament is to be taken orally.

The invention is illustrated by the following non-limiting Examples with reference to the accompanying drawing in which:

Figure 1 represents the results of Example 1 for demonstrating the effect of a colostrum derivative on indomethacin induced damage of gastrointestinal epithelium in mice.

#### EXAMPLE 1

The effect of colostral whey on indomethacin-induced intestinal damage was assessed using a mouse model.

Mice were fed on a standard chow diet. A control group of mice (16/group) were given a placebo consisting of drinking water containing 10% (vol/vol) of defatted, microfiltered milk whey and a "colostrum" group was given drinking water that contained 10% (vol/vol) of defatted, microfiltered colostral whey. After two weeks on the respective diets, half the animals in each group also received indomethacin (8.5mg/kg subcutaneously) for a further 24 hours to induce intestinal injury. After this time the animals were sacrificed and intestinal villus height measured. Referring to Fig. 1, there was no significant difference in villus height between animals that had received colostral extract (1) and those just given placebo (2) (controls) which had not received indomethacin. Indomethacin caused significant damage (measured as a reduction in villus height) in control groups (3). However, no significant damage (\*\* in Fig. 1) occurred in the animals that had received 10% colostral whey in their drinking water for two weeks prior to indomethacin treatment (4).

**EXAMPLE 2****METHODS****1. *In vivo model of small intestinal injury*****Protocol:**

Mice were randomised into groups of twenty and fed on a standard chow diet *ad libitum*. The drinking water was supplemented with 10% solution of defatted colostrum or milk whey for six days. Pilot studies showed that the addition of these solutions did not affect the total volume drunk (mean 5 ml/mouse/day). Small intestinal injury was induced in half of the animals in each group by administering a single dose of indomethacin (85mg/Kg sc.). Animals were killed 24 h later. In order to assess changes in proliferation, each animal also received vincristine (1 mg/Kg i.p.) two hours prior to killing.

**Assessment of damage and proliferation:**

The wet weight of the various sections of the gastrointestinal tract were recorded and samples of the small intestine and colon (defined by their percentage length) were fixed in Carnoy's fluid and stored in 70% (v/v) ethanol. Tissues were subsequently stained with the Feulgen reaction and the crypts displayed by microdissection. The numbers of arrested metaphases in 20 crypts per animal per site were counted.

Differences in villus height (as an index of intestinal damage) were determined in various regions of the intestine by microdissecting the tissue and tracing the outline of the villi using a stereo dissecting microscope. Tracings were subsequently scanned and analysed by computer image analyses.

**2. Statistics**

Studies were assessed using a two-way ANOVA (with diet and presence of indomethacin as factors). Where a significant effect was seen ( $P < 0.05$ ), individual comparisons between groups were performed based on the group means, residual and degrees of freedom obtained from the ANOVA.

## RESULTS

The *in vivo* model of damage to gastrointestinal epithelium allows accurate quantitation of the degree of gastrointestinal injury and is used to determine the protective effects of growth factors involved in mucosal integrity and repair. In these studies, maximal damage occurs 24 hours after administration of indomethacin. Colostrum treated animals have very little damage after this time. This indicates that growth factors in colostrum reduce the degree of initial damage rather than increasing the rate of repair.

Animals which received colostrum or milk solutions but had not been given indomethacin showed no significant changes in gastrointestinal epithelium proliferation or villus morphology compared to control animals.

Indomethacin caused a 25% reduction in the proliferation rate (as determined by 2-hour metaphase assessment,  $P < 0.001$ ) of the small and large intestine in control animals and also those receiving colostrum or milk solution.

At both jejunal and ileal sites, indomethacin also caused a 25% reduction in the villus heights of control animals. Similar changes were seen in animals which had received 10% milk solution. Animals receiving 10% colostrum, however, had only about a 5% reduction in their villus height ( $p < 0.001$  compared to control animals receiving indomethacin). This shows that colostrum prevents damage from occurring to gastrointestinal epithelial cells.

This model demonstrates the value of colostral growth factors in preventing gastrointestinal damage. Addition of colostrum, but not milk, to the drinking water of mice markedly reduced the amount of small intestinal injury caused by indomethacin.

CLAIMS

1. The use of colostrum or a derivative thereof for the manufacture of a medicament for prophylactic treatment of a gastrointestinal condition partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug.
2. The use according to claim 1 wherein the colostrum or derivative thereof is of bovine origin.
3. The use according to claim 1 or 2 wherein the colostrum is obtained in the first 48 hours post parturition.
4. The use according to any one of claims 1 to 3 wherein the colostrum is obtained from the first and / or second milking post parturition.
5. The use according to any one of claims 1 to 4 wherein a colostrum derivative is used and is in a spray dried form.
6. The use according to claim 5 wherein 0.1- 60.0 grammes of the spray dried derivative is administered daily.
7. The use according to any one of claims 1 to 4 wherein a colostrum derivative is used and is a liquid reconstituted from a spray dried colostrum derivative.
8. The use according to any one of claims 1 to 4 wherein a colostrum derivative is used and that derivative is colostral whey or a colostral whey derivative.
9. The use according to claim 8 wherein the colostral whey derivative is obtained by ultrafiltration or microfiltration.

10. The use according to claims 8 or 9 wherein 30 - 300mls of colostral whey or colostral whey derivative is administered daily.
11. The use according to any preceding claim wherein a colostrum derivative is used and that derivative is defatted.
12. The use according to any preceding claim wherein colostrum or a derivative thereof is administered by an enteral route.
13. The use according to claim 12 wherein colostrum or a derivative thereof is administered by an enema, a nasogastric tube, gastrostomy tube or jejunostomy tube.
14. The use according to claim 12 or 13 wherein the colostrum, or derivative thereof, is administered in the form of a capsule or liquid.
15. The use according to claim 12 wherein colostrum or a derivative thereof is administered by an oral route.
16. The use according to claim 15 wherein the colostrum, or derivative thereof, is administered in the form of a tablet, capsule, liquid, food product or drink product.
17. The use according to claim 16 wherein the food product or drink product contains at least one of carbohydrates, a nitrogen source, vegetable oils, emulsifiers, oils containing long chain fatty acids, antioxidants, vitamins, soluble fibre, minerals and flavouring.
18. The use according to any preceding claim wherein colostrum or a derivative thereof is administered from 6 to 72 hours in advance of the non-steroidal anti-inflammatory drug.

19. The use according to claim 18 wherein colostrum or a derivative thereof is administered from 24 to 48 hours in advance of the administration of the non-steroidal anti-inflammatory drug.
20. The use according to any one of claims 1 to 19 wherein the non steroidal anti-inflammatory drug is one of indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac and aspirin.
21. A method for the prophylactic treatment of a gastrointestinal condition that is at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug, the method comprising administering to a person or animal in need of such treatment a therapeutically effective amount of colostrum or derivative thereof.

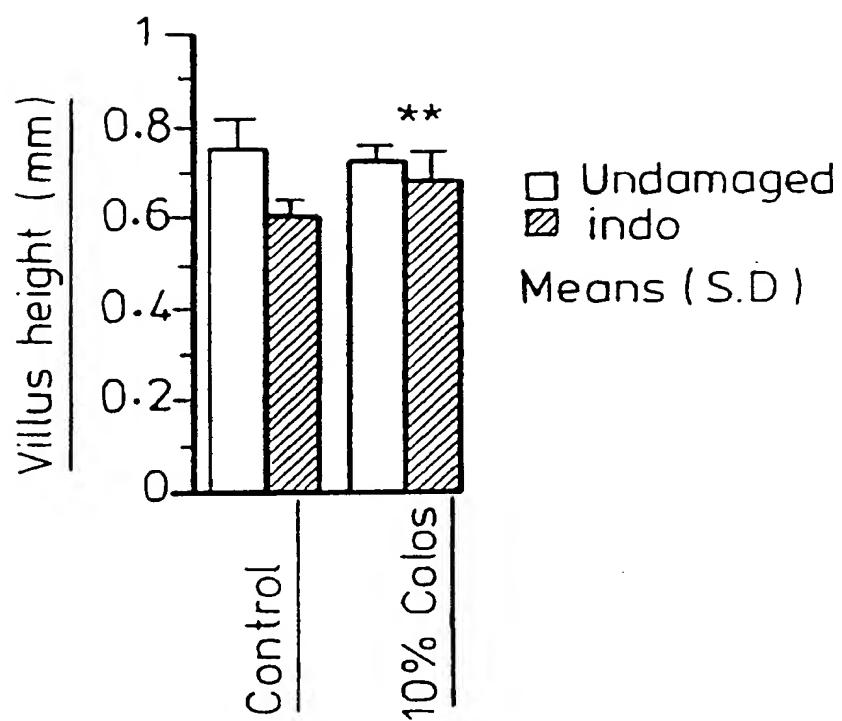
1-1

FIG. 1

**INTERNATIONAL SEARCH REPORT**

Internat'l Application No
PCT/GB 97/02572

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K35/20

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 96 34614 A (GROPEP PTY. LTD.) 7 November 1996 see the whole document ---	1-21
X	WO 95 00155 A (VALIO BIOTUOTFEET OY) 5 January 1995 see page 2, line 28 - line 32 see page 3, line 13 - line 28 see page 5, line 19 - line 28; claims ---	1-21
X	EP 0 527 283 A (SOCIETE DES PRODUITS NESTLE S.A.) 17 February 1993 see the whole document ---	1-21
X	EP 0 338 229 A (BIOTEST PHARMA GMBH) 25 October 1989 see page 2, line 1 - line 6 see claims 1-5, 21; example 14 ---	1-21
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

30 January 1998

Date of mailing of the International search report

23.02.98

Name and mailing address of the ISA

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Authorized officer

Ryckebosch, A

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/GB 97/02572

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 484 148 A (IMMUNO JAPAN INC.) 6 May 1992 see page 2, line 1 - line 18 see page 5, line 33 - line 54 see page 6, line 55 - page 7, line 17; claims; examples 1,2,5 ---	1-21
A	WO 92 02538 A (PROCOR TECHNOLOGIES, INC.) 20 February 1992 see the whole document ---	1-21
Y	WO 93 14783 A (I. PARIKII ET AL.) 5 August 1993 see page 3, line 19 - line 27; claims 41-43 see page 12, line 21 - page 17, line 23 ---	1-21
Y	CHEMICAL ABSTRACTS, vol. 111, no. 1, 3 July 1989 Columbus, Ohio, US; abstract no. 1522u, S. SUZUKI : "HUMAN EPIDERMAL GROWTH FACTOR IN BREAST MILK, EARLY NEONATAL URINE, AND AMNIOTIC FLUID: SPECULATION ON THE SOURCE AND PHYSIOLOGICAL ROLE." page 152; XP002053998 see abstract & NAGOYA MED. J., vol. 33, no. 2, 1988, pages 91-110, ---	1-21
A	CHEMICAL ABSTRACTS, vol. 103, no. 11, 16 September 1985 Columbus, Ohio, US; abstract no. 82348b, L. JANSSON ET AL.: "MITOGENIC ACTIVITY AND EPIDERMAL GROWTH FACTOR CONTENT IN HUMAN MILK." page 121; XP002053999 see abstract & ACTA PAEDIATR. SCAND., vol. 74, no. 2, 1985, pages 250-253, ---	1-21
		-/-
2		

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/GB 97/02572

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	R.J. PLAYFORD ET AL.: "BOVINE COLOSTRUM IS PROPHYLACTIC AGAINST INDOMETHACIN-INDUCED INJURY." GASTROENTEROLOGY, vol. 112, no. 4 SUPPL., April 1997, BALTIMORE, MD, US, page A394 XP002053545 see right-hand column, last abstract -----	1-21

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 97/02572

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claim 21 is directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.  
PCT/GB 97/02572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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